BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 19 NOVEMBER 1977

Heroic treatment for fulminant hepatic failure?

Fulminant hepatic failure is the clinical syndrome[1] that results from massive necrosis of liver cells or from sudden and severe impairment of hepatic function. Typically the patient has an acute onset of severe mental changes starting with confusion and advancing to stupor or coma. Jaundice appears and deepens, and there may be gastrointestinal bleeding and renal failure. Conventionally the term fulminant hepatic failure is restricted to patients in whom signs appear within eight weeks of the onset of the illness and in whom there has been no evidence of liver disease previously. In Britain viral hepatitis is the most common cause, but overdosage with paracetamol comes a close second, and various other drugs and toxins[2] may also be responsible.

Recent clinical and experimental studies have increased our understanding of the complex disturbances in fulminant hepatic failure and laid the basis for more rational treatment.[3] The encephalopathy is of central importance and its severity is closely related to the prognosis. Retention of toxic metabolites such as ammonia, mercaptans, and short chain fatty acids is probably important in its pathogenesis, while "false" neurotransmitters derived from amino-acids[4-6] have also been implicated. Conventional treatment consists in avoiding all sedatives; withdrawal of oral protein; emptying the bowels by enema; and giving oral neomycin or lactulose, or both. Cerebral oedema is found post mortem in up to 38% of fatal cases,[7] but no treatment has been shown to be effective clinically (though in animals large doses of corticosteroids given early retard the development of oedema). Hypoglycaemia occurs frequently, and restoration and maintenance of the blood sugar concentration with intravenous glucose infusions are essential. The serum electrolyte concentrations need to be carefully monitored: serious hypokalaemia may occur and requires correction. Complex changes in acid-base balance are seen, the most common being an initial alkalaemia,[8] but attempts to correct these disturbances seem to have no beneficial clinical effect. The development of renal failure is another common and serious complication, and peritoneal dialysis may be required.

Until recently gastrointestinal haemorrhage was a dreaded complication of fulminant hepatic failure. Factors in its pathogenesis include reduced synthesis of clotting factors, disseminated intravascular coagulation, and bone marrow depression. Treatment was far from straightforward: replacement of clotting factors with fresh frozen plasma did not seem to be of benefit and sometimes resulted in serious sodium overload, while giving clotting factor concentrates could precipitate disseminated intravascular coagulation.[9] Nevertheless, upper gastrointestinal endoscopy has shown that the source of bleeding is usually either erosive oesophagitis or gastritis, and prophylactic treatment with cimetidine[10] promises largely to eliminate the problem.

Endotracheal intubation may be needed early to protect the airway, and respiratory failure may require mechanical ventilation. Hypoxaemia is common even without pulmonary infection or oedema and is probably due to intrapulmonary shunts. Hypotension (in the absence of haemorrhage or fluid depletion) is another frequent problem and may lead to severe brain ischaemia, since cerebral autoregulation is lost.[11] Every effort needs to be made to maintain both the arterial Po_2 and the blood pressure.

Two other forms of treatment need to be mentioned, if only to dismiss them. Corticosteroids are still widely used, though there is neither theoretical nor clinical evidence of benefit.[12] Hepatitis B immune serum has been given in fulminant hepatic failure due to type B hepatitis, but again a large multicentre trial in the United States has shown it to have no clinical value.

The prognosis of the individual patient is difficult to assess, but the depth of coma and age are both important[13]: in one study only 18% of patients in grade IV coma survived compared with 66% in grade II, and the outlook is much better in children and young adults. Nevertheless, there have been occasional reports[14] of much higher survival rates, and this unpredictable clinical course makes uncontrolled observations extremely difficult to interpret.

These critically ill patients should be treated in an intensive care area.[3] Treatment is based on the premise that if the patient's general condition can be maintained complete recovery should be possible because of the liver's capacity to regenerate. Indeed, in survivors the liver architecture returns essentially to normal and cirrhosis is an unusual sequel.[15] Heroic measures intended to rid the body of retained toxins have therefore been tried over the years: these have included exchange transfusion, plasmapheresis, total body washout, cross-circulation, and extracorporeal liver perfusion. None has been shown to be effective, and they have largely been abandoned.[3] Haemoperfusion of charcoal columns enjoyed some popularity,[16] but no controlled trial was carried out and most

observers were sceptical of its value. Recently attention has been shifted to haemodialysis using a polyacrylonitrile membrane (which differs from standard cuprophane and cellophane membranes in allowing through compounds with molecular weight of up to 15 000). Two groups have reported results so far. In Paris Opolon[17] has treated 39 patients with coma due to fulminant hepatic failure, and, though 17 recovered consciousness, only nine survived. The group at King's College Hospital[18] has treated 24 patients: nine recovered consciousness and eight survived.

At present, therefore, we have no convincing evidence that any form of artificial liver support is able to increase the chances of survival in fulminant hepatic failure. It has been suggested that treatment should be started before grade IV coma supervenes, but such patients have, of course, a much better prognosis and the results of different types of treatment will be difficult to evaluate without a controlled trial. Meantime the best hope for survival is offered by scrupulous attention to the details of management in an intensive care unit accustomed to treating these patients.

[1] Trey, C, and Davidson, C S, *Progress in Liver Diseases*, ed H Popper and F Schaffner, vol 3, p 282. New York, Grune and Stratton, 1972.
[2] Gazzard, B G, *et al*, *Quarterly Journal of Medicine*, 1975, **44**, 615.
[3] Murray-Lyon, I M, and Trewby, P N, *Recent Advances in Intensive Therapy*, 1977, **1**, 125.
[4] Schenker, S, Breen, K J, and Hoyumpa, A M, *Gastroenterology*, 1974, **66**, 121.
[5] Zieve, L, in *Artificial Liver Support*, ed R Williams and I M Murray-Lyon, p 11. Tunbridge Wells, Pitman Medical, 1975.
[6] Fischer, J E, and Baldessarini, R J, in *Progress in Liver Diseases*, ed H Popper and F Schaffner, vol 5, p 363. New York, Grune and Stratton, 1976.
[7] Hanid, M A, *et al*, *Digestion*, 1976, **14**, 517.
[8] Record, C O, *et al*, *Gut*, 1975, **16**, 144.
[9] Gazzard, B G, *et al*, *Gut*, 1974, **15**, 993.
[10] Macdougall, B R D, Bailey, R J, and Williams, R, *Lancet*, 1977, **1**, 617.
[11] Trewby, P N, *et al*, British Society of Gastroenterology meeting, September 1977. In press.
[12] Redeker, A G, Schweitzer, I L, and Yamahiro, H S, *New England Journal of Medicine*, 1976, **294**, 728.
[13] Saunders, S J, Terblanche, J, in *Artificial Liver Support*, ed R Williams and I M Murray-Lyon, p 217. Tunbridge Wells, Pitman Medical, 1975.
[14] Reynolds, T B, *Gastroenterology*, 1969, **56**, 170.
[15] Karvountzis, G G, Redeker, A G, and Peters, R L, *Gastroenterology*, 1974, **67**, 870.
[16] Gazzard, B G, *et al*, in *Artificial Liver Support*, ed R Williams and I M Murray-Lyon, p 234. Tunbridge Wells, Pitman Medical, 1975.
[17] Opolon, P, *et al*, 12th Meeting of the European Association for the Study of the Liver. Kavouri, September 1977 Abstract.
[18] Silk, D B A, *et al*, *Lancet*, 1977, **2**, 1.

Evaluating drugs: a new approach

Last year a new approach to drug symposia was tried out at the University of Leuven. Professor M Verstraete had decided that the time had come for a detailed study of the validity of the clinical claims made for the many haemostatic drugs currently available. He invited a group of experts on haemostasis and clinical pharmacology to come together with representatives from the drug manufacturers for a critical discussion of their place in treating bleeding disorders (vitamin K, blood products, and agents for topical use were excluded from the agenda). For each commercially available haemostatic substance a report by one of the invited experts was circulated; these reports reviewed in detail the published data and the material submitted by the manufacturer, and they formed the basis of the discussion during the symposium. The published version[1] reflects the common opinion of the invited experts, though the manufacturers' representatives were given an opportunity to comment on this final report.

Rigorous criteria were adopted in examining claims for efficacy. If trials were not double-blind, with random allocation of an experimental drug and a placebo, blood loss had to be estimated quantitatively. Definition and selection of patients admitted to the trial, and the criteria for withdrawal, had to be strict and explicitly stated, and a satisfactory statistical analysis of the results was required. A clear distinction was demanded between the therapeutic and prophylactic use of haemostatic agents, and evidence was considered separately for well-defined bleeding disorders such as haemophilia and thrombocytopenia.

Nineteen reports on 64 proprietary haemostatic preparations were considered. From this large array of drugs the only two to emerge as being of proved efficacy were the antifibrinolytic agents aminocaproic acid and tranexamic acid—which were accepted as being clinically effective after prostatectomy, adenotonsillectomy, and tooth extraction, in essential menorrhagia, and after the insertion of an intrauterine contraceptive device. There also appeared to be evidence that ethamsylate was an effective haemostatic drug in primary menorrhagia. Some of the other general haemostatic agents examined probably do reduce bleeding, but the meeting concluded that their efficacy had not been finally proved in adequate trials.

The concluding section of the symposium proceedings set out in some detail recommendations on the design of clinical trials of general haemostatic agents. This conference has highlighted the inadequate clinical evidence for the use of some haemostatic drugs; its clear-cut findings suggest that the same type of analysis might be applied to many other areas of clinical pharmacology.

[1] Verstraete, M, ed, *Haemostatic Drugs: a Critical Appraisal*. The Hague, Martinus Nijhoff, 1977.

Allopurinol treatment for calcium stone disease

Urinary tract stone disease has a long history, going back to prehistoric times indeed. It has changed greatly in the last century. Whereas the stone of ancient and even recent history was predominantly a bladder stone mainly composed of ammonium urate, the common stone of today presents in the upper urinary tract and is composed mainly of calcium salts, particularly calcium oxalate.[1]

The risk of forming these stones seems to be determined by the ratio of calcium oxalate saturation (largely a reflection of the calcium and oxalate concentrations) to inhibitory activity in the urine:[2] that is, one may have a high concentration of calcium oxalate with impunity if it is balanced by a high concentration of the natural inhibitors of crystal growth and aggregation. Thus two approaches to treatment are possible: reducing calcium oxalate and increasing the inhibitory activity in urine.

Most treatments for calcium oxalate stone disease have come into the first category, being aimed at reducing calcium or oxalate excretion, or both. They include a low-calcium, low-oxalate diet,[3] thiazide diuretics,[4 5] and phosphate supplements[6 7]—all of which are said to reduce the rate of recurrence.